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Hs-CRP Levels In Adolescents With Obesity And Non-Obesity

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ABSTRACT

Increased hs-CRP levels are a response to increased cytokine secretion in fat tissue in obese adolescents so that it can be used as a risk marker for disease. The study aims to determine the value of hs-CRP levels in obese and non-obese adolescents in middle and high schools in Makassar, South Sulawesi. The design of this research is analytical research with a cross-sectional design. The research sample was adolescents with obesity and non-obese in junior and senior schools in Makassar, South Sulawesi. Data were analyzed using the chi-square test, Mann-Whitney test, and ROC curve analysis. This research obtained 150 adolescents. The average hs-CRP level in obese adolescents was 10.60 mg/L. The average hs-CRP level in non-obese adolescents was 2.06 mg/L. From the statistical test results, it was found that the p-value (0.000) was <0.05, which means that there was a difference in mean hs-CRP between the obese and non-obese categories. The results of the ROC analysis obtained a cut-off of 6.53 mg/dl. The area under curve (AUC) value is 0.945 which is in the strong category in predicting the risk of cardiovascular disease in obese and non-obese adolescents. The sensitivity value is 93.48% and the specificity is 93.10%, hs-CRP ⩾ 6.53 mg/dl can predict risk factors for cardiovascular disease in obese adolescents by 57.61% and predict non-risk factors in non-obese adolescents by 56.90%. hs-CRP levels can be a marker of cardiovascular disease in obese adolescents.

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1. INTRODUCTION

The prevalence of obesity in the world is still high, according to the World Health Organization (WHO), 2016 the number of children under 5 years who are overweight has reached more than 41 million children throughout the world, half of the population of obese children came from Asian countries including Indonesia. Obesity in children is still a problem, one in ten adolescents in the world is obese and the increase in obesity in children and adolescents is currently parallel to that of adults.1 The prevalence of nutritional status (BMI/U) in children aged 5-12 years in Indonesia showed that the obesity rate in South Sulawesi was 4.2%.2

Obese children and adolescents are at high risk of developing a variety of health problems and are also more likely to become obese adults. Obesity in childhood also has several risk factors for cardiovascular disease (CVD) in adulthood due to the development of vascular inflammation and the development of changes in the arterial walls.3

In obesity, the accumulation of adipose tissue can trigger an increase in pro-inflammatory agents. The greater the area of adipose tissue and the volume of adipocytes, the greater the pro-inflammatory agents, such as in obese sufferers. High-sensitivity C-reactive protein (hs-CRP) has recently emerged as a useful bio-marker for vascular inflammation associated with atherosclerosis. Of the novel risk factors for cardiovascular disease currently under investigation, high-sensitivity C-reactive protein hs-CRP is the most promising. To date, more than 20 prospective epidemiological studies have demonstrated that hs-CRP independently predicts vascular risk. Increased hs-CRP levels in response to increased adipose tissue cytokine secretion in obesity can be used as a marker of cardiovascular risk.4

Research in India in children 6-16 years old showed that hs-CRP levels increased significantly in overweight and obese children compared to children who were not obese. Obese children show abnormalities in lipid and glucose metabolism.5 Research in Japan on children 6-11 years old showed that hs-CRP levels increased in obese children. Obesity became a predictor of obesity after 12 months.6

The subjects in this study were adolescents aged 11-18 years, this is by data from the World Health Organization which shows that obesity rates will be high in 2022, especially adolescents of middle school and high school age. The causes of obesity in school-age adolescents are very diverse, ranging from high consumption of sugar, salt, and fat, lack of education about healthy nutrition at home and school, availability of instant and fast food with low nutrition but cheap prices to the increasing physical activity of adolescents and adolescents. A little. The aim of comparing hs-CRP levels is to prove the hypothesis that hs-CRP is higher in obese adolescents so that researchers can provide education regarding complications that will occur in obese adolescents and obesity management. This research is the first in South Sulawesi, comparing hs-CRP levels in groups of obese and non-obese adolescents aged 11-18 years, so it requires a lot of research so that this research can run well.

2. METHOD

Study design

This research is an analytical study with a cross-sectional design to compare hs-CRP levels in obese and non-obese adolescents. The research was carried out based on the approval of the ethics committee for biomedical research on humans, Faculty of Medicine, Hasanuddin University, and RS Wahidin Sudiohusodo Makassar No.

Data collection

The sample for this research is obese and non-obese adolescents aged 11 to 18 years spread across middle and high schools with middle to upper economic status based on criteria determined by the Makassar City Education Office. How to take samples using Multistage Cluster Proportionale Random Sampling. Researchers obtained data from the Makassar City Education Office regarding middle and high schools that have students with middle to upper socioeconomic levels. After the cluster of schools with a middle to high socioeconomic level was obtained, random school selection was carried out to select the schools that would be used as research sites. The inclusion criteria were obese and non-obese adolescents aged 11-18 years who were enrolled in private junior and senior high schools in the city of Makassar and whose parents agreed to participate in the research. Exclusion criteria are obese adolescents who have a history of impaired liver and/or kidney function, obesity due to genetic or chromosomal abnormalities such as Prader-Willi Syndrome, endogenous obesity, endocrinological disorders such as hypoparathyroidism or hyperparathyroidism and diabetes mellitus, long-term corticosteroid treatment, cytostatics or other drugs, and adolescents were sick or absent and therefore did not take part in the study.

Variable

The data collected includes demographic data in the form of age, gender, education, and pubertal status. Nutritional status data is measured based on body mass index (BMI) through measurements of body height and weight. Blood levels of hs-CRP were measured using an ELISA kit.

Statistic analysis

Data were analyzed using the chi-square test and Mann-Whitney test as well as diagnostic tests with the ROC curve analysis. In statistical tests, a p-value of less than 0.05 is declared significant. Data were analyzed with IBM SPSS version 25.

3. RESULTS AND DISCUSSION

The research found 150 adolescents, of which 92 adolescents (61.33%) were obese and 58 adolescents (36.67%) were not obese. A comparison of the characteristics of obese and non-obese adolescents shows that there is no significant difference in gender and Tanner in the two groups with a p-value > 0.05, but there is a significant difference in education level in the two groups with a p-value < 0.05 (Table 1).

Table 1. Subject characteristics based on nutritional status

Characteristics	Nutritional Status						p-value
	Obese (n= 92)		Non-obese (n= 58)		Total		
	n	%	n	%	n	%	
Gender							
Male	55	67.9	26	32.1	81	100	0.105
Female	37	53.6	32	46.4	69	100	
Education							
Junior high school	75	70.1	32	29.9	107	100	0.001
Senior high school	17	39.5	26	60.5	43	100	
Tanner							
1	1	100	0	0	1	100	
2	9	45	11	55.0	20	100	
3	31	53.4	27	46.6	58	100	0.052
4	29	65.9	15	34.1	44	100	
5	22	81.5	5	18.5	27	100	

Uji Chi-Square

The relationship between nutritional status and hs-CRP, of the 92 obese adolescents, none had low hs-CRP levels, 4 obese adolescents had moderate hs-CRP levels (12.9%) and 88 obese adolescents had high hs-CRP levels (91.7%), while of the 58 non-obese adolescents, 23 adolescents had low hs-CRP levels (100%), 27 adolescents had moderate hs-CRP levels (87.1%), 8 adolescents had high hs-CRP levels (8.3%). The statistical test results show that there is a very significant relationship between nutritional status and hs-CRP levels with a p-value <0.05 (Table 2).

Table 2. Relationship between hs-CRP and nutritional status

hs-CRP	Nutritional status						p-value
	Obese		Non-obese		Total		
	n	%	n	%	n	%	
Low	4	0.0	23	100.0	23	100	0.000
Medium	88	12.9	27	87.1	31	100	
High	92	91.7	8	8.3	96	100	

Uji Chi-Square

A comparison of hs-CRP levels between obese and obese adolescents shows that there is a very significant difference in mean hs-CRP between obese and non-obese adolescents with a p-value <0.05. The average hs-CRP in obese adolescents was 10.60 mg/L, higher than in non-obese adolescents at 2.06 mg/L. A comparison of the ages between obese and obese adolescents shows that there is a very significant difference in the average age between obese and non-obese adolescents with a p-value <0.005. The average age of obese adolescents is 13.79 years, lower than non-obese adolescents with an average of 14.91 years.

Table 3. Comparison of age and hs-CRP levels with nutritional status

Variable	Obese		Non-obese		P-value
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
hs-CRP (mg/L)	10.60 ± 2.59)	11.14 (1.21-15.15)	2.06 ± 2.82	1.13 (0.32-12.50)	0.000
Age (Years)	13.79 ± 1.51	13.50 (11.00 - 17.00)	14.91 ± 1.50	15.00 (12.00 - 17.00)	0.000

Uji Mann-Whitney

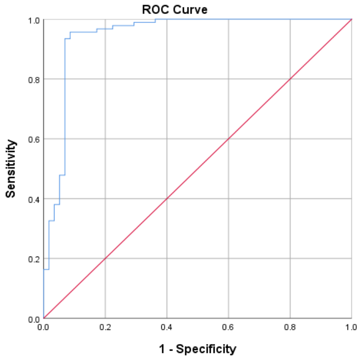

Figure 1. Receiver Operating Characteristic (ROC) curve

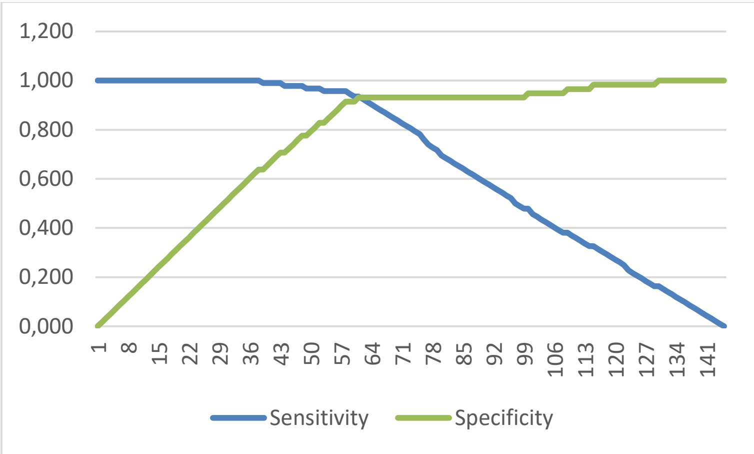

Figure 2. The cut-off curve of hs-CRP and Nutritional Status

The test results with the AUC graph in Figure 1 and the cut-off curve between hs-CRP and nutritional status in Figure 2 show that the cut-off hs-CRP for nutritional status is 6.53 mg/L. The AUC value is 0.945 which is in the strong or good category to be used as a prediction parameter for obesity in adolescents. The OR value is 193.50, which means it is a risk factor with the lowest CI value in the study being 52.20 and the highest 717, both of these values are >1 so they are risk factors for obese adolescents (Table 4).

Table 4. Results of hs-CRP cut-off with nutritional status

hs-CRP (mg/L)	Nutritional status						p-value	OR	CI 95% OR	
	Obese		Non-obese		Total				Low	Up
	N	%	n	%	n	%				
≥ 6,53	86	95,6	4	4,4	90	100	0,000	193,50	52,20	717,23
< 6,53	6	10,0	54	90,0	60	100				

The sensitivity value is 93.48% and the specificity is 93.10%, which means that hs-CRP > 6.53 mg/L can be obtained in obese adolescents, and the specificity is 93.10%, meaning hs-CRP levels < 6.53 found in non-obese adolescents (Table 5).

Table 5. Results of sensitivity and specificity of hs-CRP in predicting nutritional status

Parameter	Value
AUC	0,945
Sensitivity	93,48
Specificity	93,10
PPV	95,56
NPV	90,00

Discussion

The results of this study show that there is a relationship between gender and the nutritional status category, the male gender is mostly in the obese category, while the female gender also shows that the majority of adolescents are in the obese category. The results of this research are in line with research by Nuraini et al. that screening was carried out on adolescents aged 15-17 years in classes X, XI, and normal nutrition, 12.87% of adolescents with overweight nutritional status and 11.46% of adolescents with obese nutritional status. The obesity prevalence rate in this study is higher compared to similar studies.7 Research by Nishide et al. also found that the number of obese male adolescents (86.8%) was greater than that of female adolescents.6

The relationship between education and the nutritional status category is that most obese sufferers have junior high school education, while the average respondent's high school education is in the non-obese category. Humairoh and Nugroho in their research explained that the level of overweight or obesity in Indonesia has continuously increased, this situation is caused by changes in lifestyle which tend to be inactive, and also caused by the abundance of junk food. Most of the adolescents in the research sample predominantly consume junk food, resulting in excessive calorie levels.8

During adolescence, with an education level between junior high school, most adolescents do not know much about knowledge related to nutrition. The higher a person's level of education, the more knowledge they have. Therefore, knowledge influences patterns in consuming nutrients. People who understand the benefits of nutrients, how to provide nutrients, types of nutrients, nutrient content, frequency of nutrients, and also the amount of nutrients will try to get food that contains the right nutrients as needed by the body's metabolism. Education contributes to the influence on the level of insight or knowledge. Knowledge regarding health and nutrition is an influencing factor in forming consumption patterns.8

In the relationship between puberty and nutritional status categories, it can be concluded that all research samples experienced puberty in the obese category. Coztanso reported that every 1 kg/m2 increase in body mass index in adolescents will affect puberty by 6.5%. The occurrence of a person's puberty is influenced by the hormonal system, namely; Gonadotropin realizing hormone (GnRH), Follicle Stimulating Hormone (FSH), Luteinazing Hormone (LH). The release of the GnRH hormone is influenced by the presence of Leptin. Leptin is a hormonal protein that functions to regulate body weight, metabolic function, and reproduction, so that during puberty leptin levels will increase along with an increase in body fat which is characterized by an increase in body weight.9

This study showed that there was a very significant relationship between nutritional status and hs-CRP levels. The mean hs-CRP in the obese category was 10.60 mg/L, which was higher than the mean hs-CRP in the non-obese category, which was 2.06 mg/L. Similar results in research by Faam et al. found an increase in hs-CRP levels in obesity.10 The similar results were obtained by El-shorbagy and Ghoname that research on 100 adolescents aged 6-10 years with obesity found significantly higher hs-CRP levels compared to 50 adolescents without obesity (1.40 ± 0.78 vs 0.56 ± 0.47, $p<0.01$).11

In obesity, adipocytes produce excessive proinflammatory cytokines such as TNF-α and IL-6. Interleukin-6 will stimulate hs-CRP synthesis in the liver. High hs-CRP levels in obese adolescents and young people proved that inflammation occurred at a lower level at an early age compared to non-obese populations.12 The American Heart Association Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients without Coronary or Other Atherosclerotic Vascular Disease and the Disease Control and Prevention (CDC/AHA) determines that hs-CRP concentrations < 1.0 mg/L have a low risk of cardiovascular disease, a concentration of 1.0-3.0 mg/L indicates a moderate risk and a concentration > 3.0 mg/L indicates a high risk of cardiovascular disease. A hs-CRP level > 10 mg/L indicates an acute infection or inflammatory disease.13

Hs-CRP also upregulates angiotensin type-1 receptor (AT1-R) mRNA in vascular smooth muscle cells and increases AT1-R expression on the cell surface. Angiotensin type-1 receptor is the key to initiating atherosclerosis by stimulating the production of angiotensin-II which triggers the production of reactive oxygen species, migration and proliferation of vascular smooth muscle cells, and vascular remodeling.14 Hs-CRP also plays a role in increasing the activity of other proinflammatory adipokines such as plasminogen activator inhibitor-1 (PAI-1) in endothelial cells. PAI-1 is an acute-phase prothrombotic protein that suppresses fibrinolysis by inhibiting plasminogen activation which causes atherogenesis by triggering thrombus formation. PAI-1 levels in plasma have a positive correlation with cardiovascular risk and death.15

In general, from these results, it was found that the majority of respondents were obese and had high hs-CRP levels. Many things can influence this incident. The environmental factors play a role in causing obesity, namely nutritional (eating behavior), physical activity, trauma (neurological or psychological), medication (steroids), and socioeconomic. Obese adolescents usually come from families with obesity.16 If both parents are obese, around 80% of their adolescents will suffer from obesity. If just one parent is obese, the incidence is 40%. And if both parents are not obese, the prevalence will drop to 14%. The increased risk of becoming obese is possible due to the influence of genes in the family.17

Based on data from Basic Health Research in Indonesia, it is stated that in school-age adolescents there has been an increase in the prevalence of obesity from 7.9% in 2007 to 9.2% in 2010.2 Obesity in adolescents is an important problem to understand obesity is not only about an imbalance in energy intake and expenditure. In particular, adipose tissue is known as a passive energy storage site, now considered a major endocrine organ. Adipose cells produce several chemical signals that act on various physiological processes of the body.7

Obesity in adolescents is a risk factor for cardiovascular morbidity in adulthood. Obesity causes blood vessel inflammation associated with atherosclerosis through a low-grade inflammatory process. Several studies have shown an increase in hs-CRP in obese adolescents compared to normal adolescents. The formation of atherosclerosis itself rarely occurs before adulthood, although it begins in adolescence (with the presence of fat and thickening of the middle arteries). These fibrous plaque lesions were surprisingly found in the coronary arteries of as many as 33% of adolescents who died suddenly from autopsy results.

In terms of age, the average age in the obese category is 13.79 years, while the average age in the non-obese category is 14.91 years. There is a significant difference in age between the obese and non-obese categories. The National Health and Nutrition Examination Survey (NHANES) states that obesity is increasing at all stages of adolescence, both boys and girls and also without ethnic, ethnic or racial limitations. However, approximately 90% of obesity cases are idiopathic; and only 10% are related to genetics and hormonal disorders.18

This research then also tested the hs-CRP parameter in predicting risk factors based on nutritional status, obtaining a cut-off point value for hs-CRP levels of 6.53 mg/L with a sensitivity of 93.48% and a specificity of 93.10%. hs-CRP can predict the occurrence of obesity in obese and non-obese adolescents. The high levels of hs-CRP in this study were found in obese adolescents, this was due to an inflammatory response from energy stores which produced excess adipose tissue in obese adolescents. This condition triggers the activation of pro-inflammatory cytokines which can trigger the formation of CRP in the liver. Based on the inflammatory theory, obesity occurs when the balance of adipocytokines is released occurs. Adipocyte cells try to maintain energy balance by releasing IL-6, TNF α, and Monocyte Chemoattractant Protein-1 (MCP-1). The release of these cytokines marks the beginning of inflammation. Obesity can be said to be a form of chronic inflammation. Interleukin 6 and TNF α can trigger the formation of CRP in the liver.19,20

The formation of CRP can be detrimental to the arterial wall because it increases inflammation in endothelial cells.21 Based on the researchers' analysis, there is a difference in hs-CRP levels in BMI with obesity, which is higher than normal, because the inflammatory response that occurs as a result of energy stores that produce adipocytokines from obese sufferers can trigger a form of chronic inflammation. This condition triggers the activation of pro-inflammatory cytokines, namely Interleukin 6 and TNF α, which can trigger the formation of CRP in the liver. Therefore, the results of this study emphasize that a weight loss program in obese adolescents can affect reducing pro-inflammatory cytokines and hs-CRP levels which are directly proportional to weight loss. Specifically, individuals who have hs-CRP levels higher than normal levels will have four times the risk compared to individuals who have normal or low values. The American Heart Association and the US Centers for Disease Control and Prevention divide risk groups as follows: low risk if the level is less than 1.0 mg/L, medium risk if the level is 1.0-3.0 mg/L, and high risk if the level is above 3.0 mg/L.22

The strength of this research is that it carried out early screening for the risk of cardiovascular disease in obese and non-obese adolescents from school age so that prevention could be carried out earlier. A limitation of this study was that screening for acute inflammation or allergies that had occurred before measuring hs-CRP levels was not carried out so that moderate and high hs-CRP levels were still found in non-obese adolescents. This is supported by research that hs-CRP levels will increase up to 100 mg/L if a bacterial infection occurs, while hs-CRP levels will increase <10 mg/L in viral infections within 48 hours and last for 18 hours.23 Another limitation is that it is not known how long the obesity process occurs in adolescents because this research was conducted cross-sectionally.

4. CONCLUSION

Adolescents with obesity have hs-CRP levels that are significantly higher than non-obese adolescents. The hs-CRP level as a predictor of the risk of cardiovascular disease in obese adolescents with a cut-off of 6.53 mg/L a sensitivity value of 93.48% and a specificity of 93.10%. This research has implications for efforts to prevent and early diagnose obesity in adolescents. Further research can identify several supporting variables, such as smoking intensity, alcohol consumption, daily lifestyle, family history, and the course of obesity.

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